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10/694,448	10/27/2003	Kathleen C.M. Campbell	SIU 7398	8896

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EXAMINER
ANDERSON, JAMES D

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/694,448	CAMPBELL, KATHLEEN C.M.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-33,35,36 and 38-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-33,35,36 and 38-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-5, 7-33, 35-36, and 38-45 are presented for examination

Applicants' amendment filed 1/9/2008 has been received and entered into the application. Accordingly, claims 1, 31, and 33 have been amended.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Applicant's arguments filed 1/9/2008 have been fully considered but they are not persuasive. With respect to the 35 U.S.C. 103 rejection of claims 1, 3-5, 8, 10-17, and 19-32 as being unpatentable over Basinger *et al.*, Applicant presents the following arguments.

Firstly, Applicant argues that the claims recite a method of reducing the incidence of ototoxicity while the cited reference teaches methods for reducing the incidence of nephrotoxicity. As such, Applicant asserts that the claims are patentable over Basinger *et al.* However, while Basinger *et al.* only studied the effects of methionine administration on the reduction of cisplatin induced nephrotoxicity, the reference teaches that ototoxicity is a dose-limiting toxicity associated with cisplatin. As such, combined administration of cisplatin and methionine with naturally result in a decrease in the incidence of ototoxicity induced by cisplatin as recited in the instant claims. In this regard, the same patient population is being administered the same active agents. As such, the effects of such administration are properties of the

combined active agents and are not separable therefrom. In other words, the prior art provides clear motivation to administer methionine in combination with cisplatin so as to reduce nephrotoxicity.

Secondly, Applicant argues that administration of an inherently ototoxic dosage of cisplatin cannot be demonstrated in any method suggested by the cited reference. However, the cited reference explicitly teaches that ototoxicity is a dose-limiting toxicity associated with cisplatin therapy. Further, and perhaps more importantly, the claims do not recite a patient population having ototoxicity. The claims only require a patient undergoing treatment with a chemotherapeutic amount of an anti-tumor platinum coordination compound. Reducing the incidence of ototoxicity is recited as a claimed effect of administration of methionine to said patients. As such, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to administer of methionine to a patient undergoing treatment with a chemotherapeutic amount of an anti-tumor platinum coordination compound as taught in Basinger *et al*. A reduction in dose-limiting toxicities would have been a natural result of such administration.

Claim Rejections - 35 USC § 112 (2nd Paragraph) (New Ground of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. Claim 41 recites the limitation "said anti-tumor platinum-coordination compound" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112 (1st Paragraph)(New Ground of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-22 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for topically applying an otoprotective agent to the round window membrane of a patient, does not reasonably provide enablement for orally or parenterally administering an otoprotective agent to the round window membrane of a patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

Upon further consideration, it is not clear how one could parenterally or orally administer an otoprotective agent to the round window membrane of a patient. Parenteral administration involves injection (*e.g.*, intravenous or intramuscular). Oral administration involves ingestion of an active agent through the alimentary canal. However, the round window membrane of a patient is a membrane associated with the connection between the inner ear and the middle ear. As such, it is unclear how one could administer a compound *via* oral or

parenteral administration to the round window membrane of a patient. Applicants have provided no guidance or direction with respect to how one skilled in the art could administer an otoprotective agent to the round window membrane of patient via oral or parenteral administration of said otoprotective agent. In fact, Applicants only disclose in the specification topical administration to the round window membrane of the ear (page 45, lines 21-25).

Claim Rejections - 35 USC § 102 (New Ground of Rejection)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33, 35, 36, and 38-45 are rejected under 35 U.S.C. 102(b) as being anticipated by **Furuno *et al.*** (USP No. 3,962,429; Issued June 8, 1976).

The instant claims recite methods of reducing ototoxicity in patients undergoing treatment with an aminoglycoside antibiotic comprising administering an effective amount of methionine.

Furuno *et al.* teach methods of reducing side effects (*e.g.*, renal and 8th nerve toxicities) of aminoglycoside antibiotics comprising administering a glucosaccharic acid as well as the aminoglycoside antibiotic to a patient (Abstract). In the methods of the invention, the glucosaccharic acid may be administered simultaneously with or at different times from the aminoglycoside antibiotic (col. 2, lines 22-25).

With respect to methionine as recited in the instant claims as an otoprotective agent, Furuno *et al*. teach that glucosaccharic acids are not stable so methionine is preferably added to parenteral injections containing glucosaccharic acids as a stabilizer (col. 2, lines 56-58).

With respect to an otoprotective agent that "comprises methionine", Furuno *et al*. teach compositions comprising methionine, which is reasonably interpreted as at least a racemic mixture of D and L isomers. Such a mixture "comprises" L-methionine as recited in claim 36.

With respect to the timing of administration as recited in claims 41-45, it is noted that all of these claims encompass simultaneous administration, which is clearly taught in Furuno *et al*.

The reference thus teaches administration of compositions "comprising" administration of an effective amount of methionine to patients undergoing treatment with an aminoglycoside antibiotic as recited in the instant claims. A composition comprising a glucosaccharic acid and methionine as taught in Furuno *et al*., administered to a patient taking an aminoglycoside antibiotic, meets the limitations of the instant claims.

With respect to the claimed reduction in ototoxicity, it is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc*., 339 F.3d 1373, 1377, 67 USPQ2d 1664,

1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

Though Furuno *et al.* does not expressly teach reducing the incidence of ototoxicity in a patient undergoing treatment with an aminoglycoside antibiotic as a result of the administration of a composition comprising a glucosaccharic acid and methionine, the administration of the same compound(s) as claimed to the same host as claimed is considered to necessarily have the claimed effect of reducing ototoxicity on the subject being treated, whether expressly recognized by Furuno *et al.* or not. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host. Please reference MPEP §2112.

The explanation of an effect obtained when using a composition cannot confer novelty on a known process if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. In other words, even if the reducing the incidence of ototoxicity effect was not itself recognized as a pharmacological effect of administering the disclosed compositions of Furuno et al. for the disclosed therapeutic purpose(s) discussed therein, such an effect is not considered a new therapeutic application because a known therapeutic effect (i.e., reducing toxicities such as renal and 8th nerve toxicities) and benefit of using this same active compound(s) was already known in the prior art.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-5, 7-17, and 23-32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Basinger *et al***. (Toxicology and Applied Pharmacology, 1990, vol. 108, pages 1-15) (cited by Applicant in IDS filed 2/28/2005).

The instant claims recite methods of reducing the incidence of ototoxicity in a patient undergoing treatment with a platinum-coordination compound comprising administering methionine. Claims 7 and 9 have been added to the rejection set forth in the previous Office Action and claims 19-22 are no longer rejected under this statute. Claims 19-22 recite administration to the "round window membrane" of the patient. In view of the disclosure of Basinger *et al*., it would not have been obvious to administer methionine to the round window membrane of a patient because such administration would not be effective for the treatment methods taught in Basinger *et al*.

Basinger *et al*. teach that *cis*-platinum (CDDP) is an effective antitumor compound whose administration leads to does-limiting toxicities such as nephrotoxicity, myelosuppression,

gastrointestinal toxicity, nausea, ototoxicity, peripheral neuropathies, and anaphylactic reactions (page 1, left column). Comprehensive studies of thiols and thioethers provide evidence that such compounds provide renal protection without altering the antineoplastic activity of CDDP (page 2, left column). In this regard, D-methionine, L-methionine, and some of their derivatives were the most effective agents studied (*id.*). In the present study, the authors examined the effects of L-methionine on CDDP nephrotoxicity in rats to determine the degree of renal protection obtained when the ratio of L-methionine to CDDP was varied (*id.*). Thus, CDDP and methionine were simultaneously administered to rats bearing Walker 256 carcinomas. Such administration renders obvious the combined simultaneous *i.v.* administration of a platinum-coordinating compound and methionine as recited in instant claims 1, 3-5, 8, and 10-17. A 20:1 molar excess of L-methionine to CDDP was simultaneously administered to Sprague-Dawley rats (page 2, right column). This ratio renders obvious the ratios recited in instant claims 23-26. With respect to the dosage of L-methionine recited in instant claims 31-32, Basinger *et al.* teach the administration of varying mole ratios of methionine to CDDP wherein the CDDP is administered in doses of 7.5 mg/kg to 56 mg/kg. The authors conclude that the results obtained clearly indicate that the co-administration of L-methionine and CDDP results in a very significant decrease in the nephrotoxicity found with the CDDP alone and that such treatment results in antitumor activity (page 9, right column).

Scope and Content of the Prior Art:

In the instant case, Basinger *et al.* teach that co-administration of L-methionine and CDDP to rats having Walker 256 carcinomas results in both antitumor activity and reduced nephrotoxicity. The doses administered are within the instantly claimed dose ranges and ratios.

Differences Between Prior Art and Claims:

The administration of L-methionine and CDDP to rats as taught in Basinger *et al.* differs from the instant claims in two ways. Firstly, the instant claims recite administration to humans, cats, or dogs. Basinger *et al.* teach administration to rats, a common preclinical animal model. Secondly, the instant claims recite a method of reducing ototoxicity resulting from administration of a platinum-coordinating compound such as CDDP. Basinger *et al.* only evaluated the effect of the combined therapy on nephrotoxicity, although they do teach that ototoxicity is a known side effect of CDDP therapy.

Level of Ordinary Skill in the Art:

A person having ordinary skill in the art at the time of the present invention would generally be a physician or pharmacologist having several years of experience in drug administration and toxic effects thereof.

Objective Evidence and Motivation:

In light of the above findings relating to the three *Graham* factors, the skilled artisan would have been motivated to administer methionine in combination with CDDP to other mammals in order to reduce the nephrotoxicity caused by CDDP treatment. See, *e.g.*, *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." (emphasis in original)). In this case, Basinger *et al.* explicitly teach that the claimed compound is effective in reducing nephrotoxicity associated with CDDP therapy in rats. As such, testing

the combined therapy in other animal models would be the next logical step, with a reasonable expectation that a reduction in nephrotoxicity associated with CDDP treatment would occur in other mammals.

With respect to claims 7 and 9, which recite administration of the otoprotective agent (*i.e.*, methionine) prior to or subsequent to the administration of the anti-tumor platinum-coordination compound, while Basinger *et al.* teach simultaneous administration, it is well within the purview of the skilled artisan to adjust the timing and administration regimens of prior art administration methods so as to elicit the safest and most tolerable treatment. As such, given the efficacy of simultaneous treatment disclosed in Basinger *et al.*, one skilled in the art would reasonably expect that administration of methionine prior to or subsequent to CDDP would also be effective in protecting the subjects from nephrotoxicity.

With respect to the instantly claimed effect of such combined therapy (reducing the incidence of ototoxicity), CDDP therapy is known in the art to result in ototoxicity. As such, administration of methionine to animals receiving CDDP will naturally result in the claimed effect because a compound or composition and its properties are not separable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In this case, a composition comprising CDDP and methionine administered to a patient undergoing CDDP therapy will naturally result in a reduction "in the incidence of ototoxicity". As discussed *supra*, the claims do not require that a patient have ototoxicity, or even that they will eventually develop ototoxicity. The fact that Basinger *et al.* did not monitor the animals for such an effect is not pertinent to the present rejection. The motivation to co-administer methionine and CDDP to animals undergoing CDDP therapy is explicitly found in the prior art – such co-administration results in decreased

nephrotoxicity. There may very well be other beneficial effects of such treatment (as Applicant is now claiming), but the Examiner questions how the patient population being instantly treated differs from a patient population generally being administered CDDP. Nephrotoxicity, ototoxicity, myelosuppression, gastrointestinal toxicity, nausea, etc. are all side effects of CDDP therapy as evidenced in Basinger *et al*. Thus, if one skilled in the art is motivated to administer methionine to patients receiving CDDP in order to decrease nephrotoxicity, any other beneficial (or for that matter, detrimental) effects of such treatment will naturally result.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to administer a combination of methionine and CDDP to patients undergoing CDDP therapy. This is especially true given that methionine has been demonstrated to lessen the nephrotoxicity associated with treatment with CDDP. Accordingly, in the absence of a showing that a patient undergoing therapy with CDDP and developing nephrotoxicity is distinct from a patient undergoing therapy with CDDP and developing ototoxicity, the claimed methods would have been *prima facie* obvious. As noted *supra*, the effects of administering methionine and CDDP to a patient are not separable from the composition if the composition is being administered to the same patient population.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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